REMARKS

Claims 72-91 are pending in the present application. Claims 79, 80, 83-84 and 87 have been amended. In particular, Claims 79, 83 and 87 have been amended to specify that the sustained CTL response is an effector CTL response. Support for this amendment can be found throughout the specification and claims as originally filed, for example, on page 1, lines 25-28; page 18, lines 27-32; and page 19, lines 3-9. Also, Claims 80 and 84 have been amended to further recite "inflammatory reaction assay." Support for that amendment is found in the specification as filed at page 10, lines 11-13. Thus, no new matter has been added to the application by entering this amendment.

Applicants respectfully disagree with the rejections set forth in the Office Action mailed June 30, 2004, and provide the following remarks in response thereto. Applicants respectfully submit that the application is in condition for allowance.

Rejection under 35 U.S.C. § 112, first paragraph

The Office Action has maintained the rejection of Claims 80 and 84 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is characterized as a new matter rejection. In particular, the Examiner asserts that the terms "cytokine assay, immunofluorescence assay, tumor growth inhibition assay, tumor size reduction assay, inhibition of tumor metastasis, and increase in life expectancy," represent a departure from the specification and originally filed claims.

Applicants respectfully disagree with the rejection. In support of the elements found in Claims 80 and 84, the Examiner's attention is directed to the following citations in the specification. The page and line numbers refer to the page and line numbers from parent PCT application publication No: WO 99/02183A2, a copy of which is attached as Exhibit 1.

cytokine assay	Page 10 lines 31-33 and page 12 lines 6-10 (the presence of CTL can be detected as inflammation caused by cytokine release).
Immuno-fluorescence assay	Page 13 lines 11-16 (complexes can be labeled for detection, for example, with a fluorescent substance, allowing for detection by flow cytometry.").

tumor growth inhibition assay	Page 10 lines 21-24 (time for delivery in a cancer patient will be that necessary for improvement in the patient as evidenced by the rate of growth of the tumor).
tumor size reduction assay	Page 10 lines 21-24 (time for delivery in a cancer patient will be that necessary for improvement in the patient as evidenced by reduction in the size of the tumor).
inhibition of tumor metastasis	Page 15, line 28 to page 16, line 2; page 16, lines 20-33; and page 17, lines 1-4 ("There is at present no generally accepted standard therapy for metastatic melanoma. ... The method of this invention is useful for treating malignant melanoma, even at Stage IV [metastasized melanoma].").
increase in life expectancy	Page 16, line 27 to page 17, line 2 ("patients with stage IV malignant melanoma are almost invariably incurable and treatments are palliative. Patients with Stage IV malignant melanoma have a median survival time of approximately one year and only a 10% chance of long term survival. ... The method of this invention is useful for treating malignant melanoma, even at Stage IV." Life expectancy increased by sustained CTL response.)
observation of the health of the mammal	Page 10 lines 21-24 (time for delivery in a cancer patient will be that necessary for improvement in the patient as evidenced by the improvement in the overall health of the patient being tested).

As set forth above, each of the objected to claim elements is supported by the specification and claims as filed. Therefore, reconsideration and withdrawal of the instant rejection is respectfully requested.

Rejection Under 35 U.S.C. § 102

The Examiner rejects Claims 72-74, 77-84, 86-87 and 89-91 under 35 U.S.C. § 102(b). Specifically the Examiner rejects Claims 79-80, 83, 86, 87, and 90 as allegedly being anticipated by Grohmann *et al.*, *J. Immunol Methods*, 137(1): 9-15, March 1991 (Grohmann). Also, the Examiner rejects Claims 72-74, 77-84, 87, and 89-91 as allegedly being anticipated by Sadao *et al.*, translation of Locoregional Immunotherapy-Topics at the 13th and 14th Meetings of the Japanese Research Society for Surgical Cancer Immunology, *Biotherapy* 9(7):845-851 (1995) (Sadao). Applicants respectfully disagree for the reasons set forth below.

To be anticipatory under 35 U.S.C. § 102, a single reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d

1367, 1379 (Fed. Cir. 1986). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . . There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

Grohmann does not inherently disclose an effector CTL response.

The Office Action asserts that Grohmann teaches a method of obtaining a sustained CTL response in a mammal comprising injecting minute amounts of cell-free antigen such as lysate of highly immunogenic murine lymphoma cells bound to nitrocellulose directly into the lymphatic vessel such as the spleen. The Office Action merely concludes that the direct injection as taught by Grohmann inherently sustained a CTL response because the antigen is not being degraded or susceptible to metabolic clearance. The Office Action states that Applicants' previous argument was not found persuasive because the term "measure the presence and duration of CTL with *immediately available activity* or effector CTL in the animal" is not recited in the claim.

Applicants respectfully disagree with the characterization of Grohmann in the Office Action, and the conclusions stated in the Office Action regarding Grohmann's teachings. Applicants maintain that Grohmann does not teach a method of obtaining a sustained CTL response in a mammal for the reasons set forth in the previous response. Nevertheless, in the interest of advancing prosecution of the instant application, Applicants have amended independent Claims 79, 83, and 87 to specify that the sustained CTL response is "a sustained effector CTL response." Grohmann does not disclose such a sustained effector CTL response, and sustained effector CTL response would not be an inherent feature of the conditions and procedures described in Grohmann. Grohmann surgically implanted membrane-bound antigen and assessed the immune response against the membrane-bound antigen. Grohmann discloses a CD4+ T-cell-mediated delayed type hypersensitivity (DTH) response and increased CTL precursors (CTLp), neither of which demonstrates a sustained effector CTL response. Presence of a positive result from a DTH test, and increased CTLp, do not correlate with an effector CTL response, but instead generally tend to indicate existing memory T cell activity. In this case, the data in Grohmann fail to show a sustained effector CTL response, and in fact, any such response is at best unlikely using the procedures of Grohmann. Since the standard for inherency is that the

inherent feature would be present *necessarily and always*, an inherency rejection based upon Grohmann is improper.

Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Sadao is misinterpreted or mischaracterized and is not a proper basis for a § 102 rejection.

The Office Action asserts that Sadao teaches a method of obtaining a sustained CTL response in a mammal by administering an antigen such as OK-432 obtained as a component of a microorganism or tumor antigen such as MAGE-I (citing page 4) by injecting directly into the lymph nodes (citing page 13) or directly into the lymphatic system (citing pages 13 and 11) such as the spleen at a level sufficient to induce a CTL response in the mammal against cancers (citing pages 8-9). The Office Action further asserts that the reference method of direct injection to the lymph nodes or spleen inherently causes a sustained exposure of the antigen to the mammal's lymphatic system. In addition, the Office Action asserts that the reference antigen is maintained by sustained delivery of the antigen by an indwelling reservoir or intermittent replacement administration (citing page 11).

Sadao is a review paper having separate sections that report fragmentary and disparate areas of research. Sadao is thus not a "single reference" of the sort on which a rejection under § 102 can properly be based. Respectfully, the Examiner has seriously misunderstood or mischaracterized Sadao, and has thus misapplied this reference in rejecting the claims. Various fragments of unrelated research results reported in different sections of Sadao have been patched together to reconstruct the limitations of the claims. The assertions from the Office Action are addressed below.

Sadao does not anticipate the claims. As indicated above, Applicants disagree with the Patent Office's interpretation of Sadao. Sadao is a 1995 publication which purports to summarize 70 independent presentations from a two year period. As such, Sadao is not directed to a single technology or embodiment. Sadao provides generalized statements concerning the overall state of cancer immunotherapy. Sadao does not provide consistent, unified, detailed or enabling teachings of any of the procedures reported in the individual presentations, but provides a general overview of their results. The 70 presentations are summarized in a number of different sections of Sadao, as outlined below:

- Abstract (page 2)
- Introduction (pages 2-3)
- Specific Immune Mechanisms (pages 4-9)
- Nonspecific Immunomechanisms (pages 9-11)
- Suitably Choosing a Drug Delivery System for Contact Between Effector Cells and Cancer Cells with High Efficiency (pages 11-12)
- Direct Locoregional Immunotherapy Using Cytokines (page 12)
- Immunostimulants Studies (pages 13-14)
- Cancer Treatment Using Monoclonal Antibodies (MoAb) (pages 14-15)
- Conclusion (pages 15-17)

It should be noted that, perhaps other than the Abstract, the Introduction and the Conclusion, each section is discrete and does not particularly relate to any other section. A discussion in one section does not correspond to a discussion in another section. Each section summarizes discrete aspects of the 70 presentations. As discussed more fully below, the Examiner argues that the claims are anticipated by finding a combination of the claim elements in several of various unrelated and discrete sections, rather than as part of a single embodiment or technology. Thus the generalized overview and summaries disclosed in Sadao do not anticipate the instant claims.

As an initial matter, contrary to the Office Action, Sadao does not disclose the administration of MAGE-I polypeptide directly into the lymph nodes or any other lymphatic organ or vessel including the spleen. MAGE-I is discussed on page 4 of Sadao in the section on Specific Immune Mechanisms. MAGE-I is discussed because, at the time of the article, it was one the few known cancer specific antigens ("there are very few tumors where a cancer-specific antigen has been identified, such as MHC class I restrictive MAGE-I in lung cancer and melanomas."). Sadao does not describe the administration of the tumor antigen MAGE-I to any region of an animal, much less to a lymph node or to the spleen.

Further, according to the Office Action, Sadao allegedly anticipates because it discloses the administration of a biological response modifier (BRM), OK-432, "directly into the lymph nodes or directly into the lymphatic system, such as the spleen at a level sufficient to induce a CTL response in the mammal against cancers." Applicants strongly disagree. The Examiner supports this assertion by taking various passages from Sadao out of order and out of context, piecing the disparate passages together.

For example, the Examiner argues that Sadao teaches delivering antigen directly to a lymph node or to the spleen based upon the disclosure found in the Abstract, and on pages 11 (section on "Suitably Choosing a Drug Delivery System for Contact ...") and 13 (section on Immunostimulants Studies) of Sadao. However, the Abstract is not at all clear as to what was delivered into lymph nodes. The Abstract recites:

> Seventy papers concerning the subject of locoregional immunotherapy for two years starting from the 13th Meeting of the Japanese Research Society for Surgical Cancer and Immunology were presented. The subjects were head and neck cancer, breast cancer, lung cancer, gastric cancer, liver cancer, colon cancer, peritonitis carcinomatosa, and the like in humans, and experimental animal tumors. The methods for administering BRMs were injection into the tumor or into lymph nodes, or into the hepatic artery or portal vein, etc. So-called missile therapy using monoclonal antibodies for various BRMs (immunostimulants, such as OK-432, PSK and lentinan, and cytokines, such as IL-2, TNF and IFN-γ) were reported. Various attempts based on remarkable advancements in cancer immunotherapy, and recently in molecular biology have been reported to this day.

As shown above, the abstract does not specify where any particular BRM is delivered, and what results were seen because of the delivery. Further, as discussed more fully below, those of ordinary skill in the art do not consider BRMs to be "antigens." Thus, the abstract does not support the assertions from the Office Action regarding antigen delivery, and it fails to disclose all of the elements of any one independent claim.

Page 11 summarizes various studies of immunotherapy drug delivery administration systems, including delivery into the spleen, but it is not clear whether it refers to delivery of anything that would be considered an antigen. Specifically, it is not clear which actual substance Sadao refers to on the cited pages. The substance could be lentinan activated carbon particulates, or an OK-432-fibrinogen mixed solution, or an interleukin-2-fibrinogen mixed solution, or an IL-2 sustained release agent, or sustained release lentinan, or OK-432 and IL-2 fibrin gel, or TNF-alpha plus Lipiodol. None of these substances would be considered by one of skill in the art to be a CTL-inducing antigen in accordance to the instant claims. For example, lentinan is an extract of the mushroom Lentinus edodes (shiitake mushroom), interleukin-2 and TNF-alpha are cytokines, and OK-432 is a biological response modifier. Regardless of what was delivered to the spleen, Sadao provides no discussion of CTL induction or sustenance in connection with the splenic delivery.

Furthermore, Page 13 includes part V of the paper, which is entitled "Immunostimulants Studies." Under the second paragraph of this section, Sadao describes immunostimulatory action caused by the administration of biological response modifier, OK-432, into lymph nodes as opposed to subcutaneous administration, and describes the reduction in liver metastasis by administration of OK-432 into the spleen. CTL induction and/or sustenance is not described anywhere in this paper in connection with the discussion of delivery into lymph nodes and the spleen. This is not surprising as BRM administration usually is characterized, not by induction of CTL against the BRM, but instead by non-specific stimulation of the overall immune response. Furthermore, with regard to the use of OK-432, nowhere does Sadao discuss the induction or sustaining of CTL for OK-432, for example.

In order to find the CTL induction or sustenance of CTL, or the obtaining or detecting CTL elements of the claims, the Examiner refers to a completely different section of Sadao, the section on Nonspecific Immunomechanisms on pages 8 and 9, which includes a brief summary of CTLs. There is no appropriate connection between the discussion of CTL in the section on Nonspecific Immunomechanisms and the discussion of routes of administration in the section on Suitably Choosing a Drug Delivery System for Contact Between Effector Cells and Cancer Cells with High Efficiency, or in the section on Immunostimulants Studies, or in the Abstract. Nowhere in this section (Nonspecific Immunomechanisms) is OK-432 discussed. Likewise, nowhere in this section is direct administration of any antigen into a lymph node, vessel, lymphatic system, or area of high lymphatic drainage discussed in connection with the discussion of CTLs. Sadao discloses no discussion of CTL specific for OK-432. In short, there is no discussion of CTLs in connection with delivery of an antigen to a lymph node, spleen, or any other lymphatic organ/vessel. In fact, there is no disclosure of administering any antigen according to the claims.

According to the Office Action, Sadao describes sustained delivery of the antigen by indwelling reservoir or intermittent replacement administration as described on page 11 of Sadao (section entitled "Suitably Choosing a Drug Delivery System for Contact Between Effector Cells and Cancer Cells with High Efficiency"). Again, Applicants disagree. The passage generally summarizes the 70 presentations, some of which apparently described various drug delivery approaches. For example, Sadao describes "attempts at continuous administration of BRMs from an intraperitoneal indwelling reservoir in thermatology using CDDP. CDDP is also known as

"cisplatin," which is a cytotoxic heavy metal that inhibits cell replication in a nonspecific manner. It is not clear from Sadao that any BRM or antigen was continuously administered to a lymph node or spleen by the indwelling reservoir. Also, the passage on page 11 discussing intermittent replacement administration does not clarify what BRM, if any, was actually administered into the spleen. It should also be noted that some BRMs are not "antigens" in the sense of being capable of interacting with MHC and being recognized by CTL. For example, some BRMs are made up of carbohydrate, rather than amino acids, and therefore, are not recognized by CTL.

The foregoing discussion establishes that Sadao is not a proper reference on which to base a rejection of the claims under § 102. The disparate nature of the "elements" in the Sadao reference can only be selected and combined through a completely impermissible act of hindsight reconstruction of the claims. Applicants therefore respectfully request that all rejections based upon Sadao be withdrawn.

The BRMs of Sadao are not antigens.

In addition to the facts that Sadao (1) is not a proper single reference for a § 102 rejection and (2) requires a distorted and impermissible hindsight reconstruction to cobble together certain of the elements of the claims, there is yet another weakness of this reference. The focus of Sadao is entirely on the administration of agents with biological response modifier activity (BRMs). However, substances classified as BRMs are not considered "antigens" by those of ordinary skill in the art. The terms "antigen" and "BRMs" are not synonymous. For example, attached as Exhibit 1 is an article by Goldwein *et al.*, entitled "Biological Response Modifiers," (http://www.oncolink.upenn.edu/treatment/article.cfm?c=2&s=9&id=54). In the article, BRMs are divided into three categories, (1) agents that restore, augment, or modulate the patient's normal immunological mechanisms; (2) agents that have direct antitumor effects; and (3) agents that have other biologic effects, such as interference with a tumor cell's ability to metastasize or survive after metastasis, promotion of cell differentiation, or interference with neoplastic transformation in cells. Several exemplary BRM agents are described: monoclonal antibodies, interferons, interleukin-2, colony stimulating factors and tumor necrosis factors. One of ordinary skill in the art will appreciate the distinction between such agents and antigens.

Further, to one of ordinary skill in the art, an antigen is a molecule that binds to the complementarity-determining region of a B cell or T cell antigen receptor (*i.e.*, an antibody or T cell receptor (TCR), respectively). In terms of the current paradigm of immunogenicity, an antigen provides "signal one" and of course, is the target of the immune response that is induced. BRMs on the other hand may bind to a variety of other receptors (*e.g.*, toll-like receptors, pattern-recognition receptors, or cytokine receptors) and provide "signal two." BRMs serve to increase (or decrease) the response which recognizes some other molecule(s), but BRMs are generally not themselves targets of the response.

A candidate BRM that induces a response against itself would be considered an undesirable BRM. Thus, the use of one term does not suggest the other to one of skill in the art due to the profound functional differences between antigens and BRMs.

The Examiner asserts that delivery of a BRM, OK-432, directly to lymph nodes anticipates the claims. In view of the above discussion Applicants disagree, because OK-432 is not considered by those of ordinary skill in the art to be an antigen. Because a BRM is not functionally interchangeable with an antigen, Sadao cannot be interpreted to teach administration of an antigen to induce a CTL response as required by the claims. Therefore, none of the claims is anticipated by Sadao, because Sadao does not disclose delivering an "antigen" according to the claims.

Claim 72

Even with the strained application of Sadao, not all of the claim elements are found in Sadao. For example, Claim 72 recites, *inter alia*:

> delivering an antigen directly to a lymph node or a lymph vessel of the mammal at a level sufficient to induce a CTL response in the mammal; and
>
> maintaining the antigen in the mammal's lymphatic system over time sufficient to sustain the CTL response.

As discussed above, Sadao does not disclose delivering an antigen directly to a lymph node or lymph vessel at a level sufficient to induce a CTL response in the mammal. Furthermore, there is no disclosure in Sadao of maintaining antigen ... sufficient to sustain a CTL response. Therefore, Sadao does not anticipate Claim 72 or any claim that depends from it, because Sadao does not teach each and every element of Claim 72.

It should also be noted that Sadao does not inherently disclose delivering antigen ... at a level sufficient to sustain. As explained above, biological response modifiers act to boost, direct, or restore the body's normal immune (defense) system. For example, they may help recruit various immune cells. One of skill in the art recognizes that a good biological response modifier does not induce CTL against itself. If it did, it would be ineffective as a BRM. OK-432, which the Examiner argues is an antigen disclosed in Sadao as being delivered according to the claimed methods, is known in the art as a good BRM. As such, its delivery would not inherently anticipate the claims because delivery of OK-432 (or any other good BRM) would not *necessarily and always* induce CTL, including CTL specific for the BRM. On the contrary, delivery of any good BRM, such as OK-432, would be expected by those of skill in the art to *rarely or never* result in a CTL response against the BRM. Sadao was interested in immunology aimed at fighting cancer, not *Streptococcus*, from which OK-432 is derived. OK-432 was delivered as a BRM in order to intensify and boost the overall immune response against cancer cells and tumors, not to elicit CTL against OK-432. Therefore, delivery of OK-432 or any of the other BRMs does not inherently anticipate, because such delivery would not *necessarily and always* induce or sustain CTLs. Because the standard for inherency is not *rarely or never*, this inherency rejection is improper and must be withdrawn.

Claim 79

Independent Claim 79 recites, in relevant part, "delivering an antigen to a lymphatic system of a mammal at a level sufficient to induce a CTL response in the mammal"; "obtaining a sustained effector CTL response in the mammal;" and "detecting the sustained effector CTL response in the mammal. As discussed above, Sadao does not disclose delivering an antigen ... at a level sufficient to induce a CTL response. Even if Sadao were to disclose such delivery, it does not disclose obtaining or detecting a sustained effector CTL response for that antigen. For example, Sadao does not disclose obtaining or detecting a sustained effector CTL response specifically for OK-432.

Claim 82

Independent Claim 82 is not anticipated. As already discussed above, Sadao does not disclose delivering the antigen ... at a level sufficient to induce a CTL response. Even if it does,

it does not disclose maintaining the antigen ... sufficient to sustain the CTL response for a period of time that is substantially co-extensive with the desired duration of the CTL response. Besides not maintaining antigen sufficient to sustain a CTL response, Sadao simply does disclose any sort of CTL response that is co-extensive with any desired duration. This not surprising in view of the nature of Sadao as a general summary of 70 different presentations, which includes very little, if any, specific detail.

Claim 83

For reasons similar to those already discussed above, Sadao does not disclose, *inter alia*, the delivering, obtaining or detecting steps of Claim 83.

Claim 87

For reasons similar to those discussed above, Sadao does not anticipate Claim 87 because it does not disclose the delivering and maintaining steps.

In light of the foregoing, Applicants respectfully submit that Claims 72-74, 77-84, 87, and 89-91 are not anticipated by Sadao because the reference does not teach each and every element of the independent claims. Accordingly, Applicants hereby request that the rejection under this section be withdrawn.

Rejection Under 35 U.S.C. § 103

The Office Action has rejected Claims 72, 75-76, and 87-88 under 35 U.S.C. § 103(a) as being unpatentable over Sadao in view of U.S. Patent No. 6,204,250 B1 (2001), Coupey *et al.*, *Cytokine* 5(6):564-9 (1993) and Zinkernagel *et al.*, *Immunol Rev* 156:199-209 (1997).

Additionally, the Office Action has rejected Claims 72, 77, 83 and 86 under 35 U.S.C. § 103(a) as being unpatentable over Sadao in view of U.S. Patent No. 5,830,452 A (1998) and U.S. Patent No. 5,279,608 (1994).

Finally, the Office Action has rejected Claims 83 and 85 under 35 U.S.C. § 103(a) as being unpatentable over Sadao in view of U.S. Patent No. 6,037,135.

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Sadao is applied as in the rejection under 35 U.S.C. § 102(b) above. As discussed in the response to that rejection, Applicants respectfully submit that Sadao does not teach each and every limitation of the independent claims. None of the secondary references alone or combined disclose the deficient elements. Thus, the cited references do not teach or suggest all the claim limitations. Accordingly, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

There is no basis or motivation to combine the references, as antigens and biological response modifiers serve distinct purposes and are not interchangeable. Furthermore, Sadao summarized 70 presentations dealing with the use of biological response modifiers. Sadao summarized presentations that explored attempts to improve therapies by stimulating or intensifying immune responses against tumors using biological response modifiers. A person of skill in the art, considering the teachings of Sadao, would not be motivated to replace BRMs, which appear to stimulate the local immune reaction generally rather than specifically, with a peptide antigen or a nucleic acid encoding an antigen, because the antigen would not be expected to function as a good BRM. Thus neither the teachings of Sadao, nor those of any of the secondary references, can provide any motivation to make the claimed invention, nor can they provide any reasonable expectation of success in doing so.

Likewise, the combination of Sadao with the '452 patent and the '608 patent, still does not provide all of the elements of the claims. The computer delivery technology (computer-driven pump and osmotic pump) disclosed in the references does not provide the above-discussed elements that are missing from Sadao. Therefore, the claims are not obvious in view of the combination, even if made.

Finally, the combination of Sadao and the '135 patent does not render Claims 83 and 85 obvious. Even if there were a motivation to combine the references, all of the elements of the claims are not present. Furthermore, for reasons similar to those discussed above, Sadao does

not suggest replacing its BRMs, which were intended to enhance the overall immune response, with antigens of the '135 patent, which would not act similarly to the BRMs.

Accordingly, Applicants respectfully submit that the PTO has failed to establish a *prima facie* case of obviousness due to its reliance upon Sadao as a primary reference. Thus, the claims are not obvious in view of the asserted combinations of references.

In light of the foregoing, Applicants respectfully submit that Claims 72, 75-77, 83, and 86-88 are not obvious under 35 U.S.C. § 103. Accordingly, Applicants respectfully request that the rejection under this section be withdrawn.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action have been addressed and that the application is now in condition for allowance. Accordingly, Applicants request the expeditious allowance of the pending claims.

The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully requested to call the undersigned to discuss such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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EXHIBIT 1

Related Topics for Chemotherapy

- Overview
- OncoLink Rx
- Support
- Side Effects
- Ask the Experts
- News
- Infection/Neutropenia
- Conferences
- OncoLink Library
- Penn Cancer Clinical Trials
- Oncolink/Emerging Med Cancer Clinical Trials Matching
- Guide to Making Decisions About Cancer Therapy
- Make Treatment Decisions with Cancer NexProfiler™ Tools

OncoTip of the Day

eNews Monthly Newsletter

CME Continuing Medical Education

OncoLink Art Gallery
Confronting Cancer

■ **Treatment Options**

Treatment Options > Chemotherapy > Overview

Biological Response Modifiers

Joel W. Goldwein, MD, Brad Somer, MD, and the OncoLink Team
Abramson Cancer Center of the University of Pennsylvania
Last Modified: November 1, 2001

Introduction

Biological response modifiers (BRMs) are another form of chemotherapy sometimes administered to cancer patients. They modify the relationship between the tumor and the patient by strengthening the patient's biological response to tumor cells. BRMs can be divided into three major categories according to mechanism of action:

1. agents that restore, augment, or modulate the patient's normal immunological mechanisms;
2. agents that have direct antitumor effects; and
3. agents that have other biologic effects, such as interference with a tumor cell's ability to metastasize or survive after metastasis, promotic of cell differentiation, or interference with neoplastic transformation in cells.

Scientists began studying BRMs in cancer therapy in the 1960s, labeling the treatment modality *Immunotherapy*. After promising results in animal studies researchers initiated many large-scale clinical trials to stimulate cancer patients' immune systems using the bacterial agents *Bacillus Calmette-Guerin* (BCG) and *Corynebacterium parvum (C. parvum)*. The results of these trials were discouraging, so the research into immunotherapy as a possible modali for cancer treatment lost momentum.

Recent advances have prompted a renewed interest in BRMs, and today biological response modification is an important area in cancer research and treatment.

Through Art is an exhibition by people whose lives have been touched by cancer.

Today's featured work:
Quell
by Bruce Pollock

Immune System: Background

The body's immune system mounts a coordinated combination of nonspecific and specific responses to foreign substances (e.g. microbes, and certain othe toxins, called *antigens*). Both physical injury and the presence of antigens ca invoke nonspecific host defenses. These defenses include physical barriers ar chemical factors, such as the skin and mucous membranes, acidic gastric secretions, and normal intestinal flora. The "inflammatory response" is anoth nonspecific host defense that serves to control the growth of microorganisms and prevent systemic infection.

Specific immune responses are elicited by the presence of an antigen. These reactions are characterized by a memory: following the initial exposure to an antigen, specific portions of the immune system produce memory cells that promote a more vigorous response to subsequent exposures to the same antigen. These specific memory responses are generally divided into *humora* and *cell-mediated* immunity.

Humoral immunity refers to the immunity conferred by the B-lymphocyte cel produced by the lymph system. These lymphocytes, also called the *B-cells*, produce antibodies. Antibodies are small proteins that can deactivate antigen by a variety of mechanisms, usually by binding with them. Antibody-antigen interaction is specific: Only one type of antibody can interact and neutralize a specific type of antigen. This interaction then activates the "complement cascade," a system of proteins that "complements" antibody activity by destroying bacteria and helping the body rid itself of antibody/antigen complexes.

Cell-mediated immunity refers to the immunity conferred by the mutation of lymphocytes, which is thought to occur in the thymus gland. These lymphocytes, also called *T cells*, directly or indirectly destroy viruses, malignant cells, cells infected with intracellular organisms, and cells of grafte organs. Different types of T cells have different immune functions: *cytotoxic* cells directly destroy antigens; helper T cells activate the "humoral immune system" and cytotoxic T-cells; and suppressor T cells inhibit antibody production and other immune responses.

Other cells that are important in the immune response are *macrophages* and *natural killer* (NK) *cells*. Macrophages are white blood cells with a number of important functions. They bind to an antigen and "present" the antigen to undifferentiated cells (precursor cells); these, in turn, become activated and produce mature lymphocytes. Without this macrophage processing, the T an B cells could not respond to some types of antigens. NK cells are cytotoxic to tumor cells and virus-infected cells.

Many cells in the immune system produce chemicals that aid in regulating th immune response. These substances are referred to as mediators and broadl referred to as *cytokines*. Many cytokines are under study, to determine their effect on the immune system.

Types of BRM Therapy

A brief review of BRM agents currently being evaluated follows.

Monoclonal Antibodies
The use of monoclonal antibodies (MoAbs) involves the development of speci antibodies directed against antigens located on the surface of tumor cells. Samples of the patient's tumor cells are taken and processed to reveal specif antibodies to the tumor-associated antigens. In order for this approach to work, a sufficient quantity of antigens unique to the tumor cells must be present. In addition, the tumor antigens must be sufficiently different from th antigens elaborated to by normal cells to provoke an antibody response.

The antibodies can be used either alone to kill cancer cells or as carriers of other substances used for either therapeutic or diagnostic purposes. For example, chemotherapeutic agents can be attached to monoclonal antibodies to deliver high concentrations of these toxic substances directly to the tumor cells. In theory, this approach is less toxic and more effective than conventional chemotherapy because it reduces the delivery of harmful agents to normal tissues is decreased.

Monoclonal antibodies can also be used for diagnostic purposes. They may be used to carry radioactive substances to cancer cells, thus pinpointing the location of metastases previously undetected by other methods.

Despite these uses, some monoclonal antibodies have limitations. Because some monoclonal antibodies may be made using mouse antibodies, they are, themselves, foreign proteins that often trigger an immune response; thus, they can be neutralized before any therapeutic effect occurs. In addition, monoclonals may lack specificity for tumor antigens. Tumor cell antigens may not be different enough from those on normal cells to ensure only cancer cell destruction; studies have revealed that most monoclonal antibodies interact with antigens on both normal and cancer cells.

More recently, many monoclonal antibodies have been created which are only derived from human proteins. Some are already FDA-approved and many others are in clinical trials, with approval imminent. In general, they have proven useful in treatment of hematologic malignancies and lymphoma. In addition, monoclonals are in development for use against solid tumors. All of these antibodies have multiple potential applications including nuclear imagir surgical mapping, and direct therapy in multiple settings (alone, in conjunctic with chemotherapy, for treatment of metastases, in adjuvant settings, in high dose rates, etc.) In the future this field will most likely grow in importance in the war against cancer.

In the clinical setting, therapeutic monoclonal antibodies are usually given ov 4-6 hours by continuous intravenous infusion. Because of the risk of serious allergic reactions (particularly with the mouse antibodies), patients are premedicated with acetaminophen and an antihistamine and monitored closely. Emergency drugs are kept by the bedside. Potential side effects of monoclonal antibodies include dyspnea and mild wheezing, fever, chills, headache, rash, mausea, vomiting, tachycardia, and allergic reactions.

Research studies are currently underway using monoclonals for a variety of diseases, include T cell lymphoma, chronic and acute lymphocytic leukemia, melanoma, colorectal cancer, and neuroblastoma.

Interferons
Interferons (IFNs) are small proteins that inhibit viral replication and promot

the cellular (T-cell) immune response. Interferon use for cancer treatment w limited until the late 1970s, when technological advances enabled mass production of IFN.

There are currently three major types of IFNs: alpha, beta, and gamma. Eac type has similar but distinctive capabilities for altering biological responses.

Alpha-IFN was the first BRM approved by the Food and Drug Administration (FDA) in 1986. Two different manufacturers have brands of this product available. Its main indication is for use in treatment of hepatitis C, but it is currently also indicated for use in the treatment of hairy cell leukemia and AIDS-associated Kaposi's sarcoma. It has also demonstrated therapeutic effectiveness against hematologic diseases such as low-grade Hodgkin's lymphoma, cutaneous T-cell lymphoma, multiple myeloma, and chronic myelogenous leukemia. It has also proven to be somewhat effective on some solid tumors, such as renal cell cancer. Beta-interferon is currently in use for treatment of multiple sclerosis.

Interferons may produce side effects of varying frequency and intensity depending on dose, schedule, route of administration, and the type of IFN. There is currently a "once per week" formulation of INF in late clinical trials which reduces the overall side-effects experienced by patients. One of the most common side effects of IFN therapy is a flu-like syndrome. Symptoms include fever, chills, tachycardia, muscle aches, malaise, fatigue, and headaches. This reaction is extremely common during a patient's first exposure to IFN, but usually decreases in intensity with continued therapy.

Other common side effects to IFN include a decreased white blood cell count, anemia (with prolonged therapy), and decreased platelets. Gastrointestinal symptoms such as a loss of appetite, nausea, vomiting, and diarrhea may als be present. Central nervous system toxicities range from mild confusion and sleepiness to seizures. Acute kidney failure is rare, but can occur. Loss of hai may also be a problem.

Interferon can be administered by IV bolus or infusion, or intramuscular, subcutaneous, or intrathecal injection. It can also be given intranasally. Redness and irritation at the injection site may occur. Since IFN is often administered on an outpatient basis, it is essential that the patient and famil are taught the technique of administration and how to manage side effects.

Interleukin-2

Interleukin-2 (IL-2) is a substance produced by lymphocytes. In addition to being an essential factor for the growth of T cells, IL-2 augments various T-c functions and enhances NK cell function. IL-2 also activates *lymphokine-activate killer* (LAK) *cells*, which are a type of killer T cell produced when lymphocytes are incubated with IL-2. LAK cells destroy tumor cells and improve the recovery of immune function in certain immunodeficiency states Patients with renal cell cancer, melanoma, and non-Hodgkin's lymphoma hav demonstrated responses to IL-2 therapy.

The most severe toxicities result from IL-2's ability to increase capillary permeability. This may cause hypotension, ascites, generalized body edema, and pulmonary edema.

Chills and fever also frequently occur within a few hours after IL-2

administration. Headache, malaise, and other flu-like symptoms are also common. Gastrointestinal effects include nausea, vomiting, loss of appetite, diarrhea, and mucositis. Some liver dysfunction is common during therapy bu resolves once treatment is stopped. Central nervous system toxicity if manifested by lethargy, confusion, disorientation, and hallucination, anxiety, and sometimes depression. Although the effect of IL-2 on the kidneys is generally mild, renal failure can result if severe hypotension occurs. Hypotension, anemia, and a decrease in platelets are more likely with higher cumulative doses. Skin changes include redness, rash, pruritus, and occasionally skin desquamation.

Although many research studies with IL-2 require intensive supportive care in acute care settings, other current treatment regimens can be given on an outpatient basis. Patient education in these situations is especially important because patients must be alert to potential side effects that should be reported immediately.

Colony Stimulating Factors

Colony stimulating factors (CSFs) are growth factors which mediate the proliferation, maturation, regulation, and activation of granulocytes, macrophages, lymphocytes, monocytes, erythrocytes, and platelets. Many types of CSFs have been produced synthetically. Some have been approved for use and some are in various stages of clinical trials. Generally, CSFs have been named for the major cell lineage they affect: Granulocyte-macrophage CSF (GM-CSF) affects both granulocyte and macrophage lineage; granulocyte CSF (G-CSF) targets only granulocytes. These two have been FDA-approved. The main indication is for treatment of neutropenic fevers. This has been studied multiple scenarios, including the prevention of neutropenic fevers primarily or secondarily, and for use in stem cell mobilization. Other colony stimulating factors include pleuripoletin IL-3, or multi-CSF, which affects early cell lineages; and macrophage CSF (M-CSF) targets macrophage production. Neumega is an IL-11 that induces platelet growth (and has FDA approval) and was hoped to limit the amounts of platelet transfusions patients may require. Unfortunately, the outcomes data has not demonstrated it to be as efficacious as originally hoped, and therefore is not often used. Other colony stimulating factors include thrombopoetin and platelet-derived growth factor (PDGF), which have been shown to induce antibodies which created platelet resistance thus prompting their manufacturers to strongly consider removing from the market. Erythropoletin, which targets erythrocyte production, was approved the FDA in 1989 for use in anemia caused by end-stage renal disease (Epo (tm)). Another version, manufactured by Ortho Biotech (Procrit) is used to treat anemia related to cancer and cancer therapy as well and the fatigue which result.

GM-CSF and G-CSF have been administered by IV bolus, subcutaneously by daily injection, or by continuous IV infusion. G-CSF therapy has been associated with only minimal toxicity, mainly bone pain. GM-CSF produces more systemic toxicities, including fatigue, fever, muscle aches, anorexia, rash and diarrhea. Blood levels of alkaline phosphatase and aminotransferases may also be increased.

Medical use of these growth factors is an important step in understanding and manipulating the immune system. Their efficacy in the treatment of congenital hematologic diseases and their ability to reduce neutropenia during cancer

treatment, makes them important agents in the treatment armamentarium.

Tumor Necrosis Factor

Tumor necrosis factor (TNF) is a substance naturally secreted by macrophages. When activated by endotoxins, the macrophages release TNF, which then binds to receptors on cell membranes. Once bound to the cell membrane, TNF initiates cellular activity and is possibly cytotoxic to that cell.

TNF is in the early phases of clinical trials and has not yet demonstrated therapeutic effectiveness against malignant diseases. Side effects of TNF are similar to those experienced with interferon therapy, including a flu-like syndrome and soreness at the injection site. Fevers and chills are generally mild and disappear with subsequent doses of TNF.